c) washing the cells in order to remove the retroviruses that has been absorbed onto the membranes of the cells;

d) treating the cells in order to eliminate the remaining extracellular retroviruses, for example by a controlled proteolysis with trypsin;

e) preparing cytoplasmic extracts by treating the cells of step d) with an extraction buffer, for example with a buffer containing 20 mM Tris-HCl (pH7.6), 0.15 M NaCl, 5 mM $MgCl_2$, 0.2 mM PMSF, 100 U/ml aprotinin and 0.5% Triton X-100;

f) centrifuging the cells obtained at step c), for example at 1000 g, and harvesting the supernatant medium, in order to separate the retroviral proteins;

g) detecting and optionally measuring the concentration of the HIV proteins, either directly or indirectly, for example by steric hindering.

REMARKS

Formal Matters

Claims 1-23 are pending in this application. Applicant has reviewed the claims in preparation for the response to the restriction requirement, and has noticed several typographical errors in the claims. Applicants have amended claims 4-9, 14, 16-18, and 23 to correct these inadvertent typographical errors. These amendments are not intended, in any way, to change the scope of the claims, either for examination purposes, or later under the doctrine of equivalents.

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Restriction Requirement

In a restriction requirement dated December 5, 2000, the Examiner required restriction under 35 U.S.C. § 121 among the following groups:

The Examiner divided the claims into the following thirteen Groups:

I. Claim 1, drawn to P40/PHAPIII V3 loop HIV-1 receptor protein and P30/PHAPI V3 loop HIV-1 receptor protein, classified in class 530, subclass 350;

II. Claims 2-6, 9-10 and 13, drawn to V3 loop HIV receptor inhibitors comprising P95/nucleolin, P40/PHAPIII V3 loop HIV-1 receptor protein and P30/PHAPI V3 loop HIV-1 receptor protein and therapeutic compositions containing same, classified in class 530, subclass 300;

III. Claims 2, 11-13, drawn to antibodies and therapeutic compositions containing same, classified in class 530, subclass 387.1;

IV. Claim 14, drawn to a therapeutic composition containing a polynucleotide inhibitor, classified in class 536, subclass 23.5;

V. Claim 15, drawn to method of altering protein expression, classified in class 514, subclass 44;

VI. Claim 16, drawn to method for using insertion DNA for specific replacement, classified in class 514, subclass 44;

VII. Claim 17, drawn to therapeutic composition comprising antisense polynucleotides, classified in class 536, subclass 23.1;

VIII. Claim 18, drawn to method of screening inhibitors via a binding assay, classified in class 435, subclass 7.2;

IX. Claim 19, drawn to method of screening modulators via protein expression, classified in class 435, subclass 39;

X. Claim 20, drawn to method of screening protein expression via antibodies, classified in class 435, subclass 7.1;

XI. Claim 21, drawn to method of detecting gene mutation, classified in class 435, subclass 91.2;

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XII. Claim 22, drawn to nucleic acid probe, classified in class 536, subclass 24.31; and

XIII. Claim 23, drawn to method of screening inhibitors via viral proteins, classified in class 435, subclass 5.

Applicants provisionally elect to prosecute Group No. II, claims 2-6, 9-10, and 13, drawn to V3 loop HIV receptor inhibitors comprising P95/nucleolin, P40/PHAPIII V3 loop HIV-1 receptor protein and P30/PHAPI V3 loop HIV-1 receptor protein and therapeutic compositions containing same, classified in class 530, subclass 300 with traverse. Applicants further elect the species wherein the inhibitor is a fragment of P95/nucleolin.

Applicants believe that this requirement is improper. While the Examiner has alleged that the claims are drawn to independent and distinct inventions, he has not shown that it would be a burden to examine the claims together. The law requires that both (1) the inventions are independent and distinct, and (2) there would be a serious burden on the Examiner if restriction was not required. M.P.E.P. § 803. The Examiner has focused on only the first part of this two-part test. In order to properly restrict the groups, the Examiner needs to show that there would be a serious burden in examining the claims together.

Applicants believe that there would not be a serious burden in Examining the groups together as the claims are all related to the V3 loop HIV receptor. Additionally, many of the groups are classified in the same class, and would not be difficult to search together. Applicants believe it would not be a burden to examine all the claims together, especially those in groups I, II, and III, groups V and VI, groups VIII, IX, X, XI, and XIII, and groups VII and XII.

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Thus, Applicants request that the restriction requirement be withdrawn.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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GARRETT & DUNNER, L.L.P.

Dated: April 5, 2001

By: Rebecca M. McNeill
Rebecca M. McNeill
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APPENDIX TO AMENDMENT OF **APRIL 5, 2001**

Amendments to the Claims

4. (Amended) The inhibitor molecule of claim 2 which consists in a peptide or pseudopeptide which is homologous containing one or several [aminoacid] amino acid additions, deletions and/or substitutions in the [aminoacid] amino acid sequence of the inhibitor molecules according to claim 3.

5. (Amended) The inhibitor molecule according to anyone of claims 1 to 4 in which the -CONH- peptide [bound] bond is modified and replaced by a (CH_2NH) reduced [bound] bond, a (NHCO) retro inverso [bound] bond, a (CH_2-O) methylene-oxy [bound] bond, a (CH_2-S) thiomethylene [bound] bond, a (CH_2CH_2) carba [bound] bond, a (CO-CH_2) cetomethylene [bound] bond, a (CHOH-CH_2) hydroxyethylene [bound] bond, a (N-N) [bound] bond, a E-alcene [bound] bond or also a -CH=CH- [bound] bond.

6. (Amended) The inhibitor molecule according to anyone of claims 1 to 5, which is derived from the P95/nucleolin [aminoacid] amino acid sequence and chosen among the following sequences:

- the sequence beginning at the [aminoacid] amino acid in position 22 and ending at the [aminoacid] amino acid in position 44;

- the sequence beginning at the [aminoacid] amino acid in position 143 and ending at the [aminoacid] amino acid in position 171;

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- the sequence beginning at the [aminoacid] amino acid in position 185 and ending at the [aminoacid] amino acid in position 209;

- the sequence beginning at the [aminoacid] amino acid in position 234 and ending at the [aminoacid] amino acid in position 271;

7. (Amended) The inhibitor molecule according to anyone of claims 1 to 5, which is derived from the P30/PHAPI [aminoacid] amino acid sequence and chosen among the following sequences:

- the sequence beginning at the [aminoacid] amino acid in position 168 and ending at the [aminoacid] amino acid in position 182;

- the sequence beginning at the [aminoacid] amino acid in position 187 and ending at the [aminoacid] amino acid in position 222;

- the sequence beginning at the [aminoacid] amino acid in position 240 and ending at the [aminoacid] amino acid in position 249; it being understood that the proximity of the two first sequences and the two last sequences allow one of ordinary skill in the art to gather the sequences contained in two sets of sequences as follows :

- the sequence beginning at the [aminoacid] amino acid in position 168 and ending at the [aminoacid] amino acid in position 222;

- the sequence beginning at the [aminoacid] amino acid in position 187 and ending at the [aminoacid] amino acid in position 249[;].

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8. (Amended) The inhibitor molecule according to anyone of claims 1 to 5, which is the following sequence derived from the P40/PHAPII [aminoacid] amino acid sequence:

- the sequence beginning at the [aminoacid] amino acid in position 223 and ending at the [aminoacid] amino acid in position 277

9. (Amended) The inhibitor molecule according to claim 2 which comprises a polymer of an inhibitor molecule according to anyone of claims 3 to 8, that contains 2 to 20 monomer units of the [aminoacid] amino acid sequence of interest derived from the [aminoacid] amino acid sequence of either P95/nucleolin, P40/PHAPIII and P30/PHAPI, preferably 4 to 15 monomer units and more preferably 5 to 10 monomer units.

14. (Amended) A therapeutic composition comprising a pharmaceutically effective amount of a polynucleotide [a polynucleotide] coding for the P95/nucleolin, P40/PHAPIII and P30/PHAPI or one of the monomeric or oligomeric peptide inhibitor molecules according to anyone of claims 2 to 9.

16. (Amended) A method for specific replacement, in particular by targeting the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein encoding DNA, called insertion DNA, comprising all or part of the DNA structurally encoding for the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein or one of its biologically active derivatives, when it is recombined with a complementing DNA in order to supply a complete recombinant gene in the genome of the host cell of the patient, characterized in that:

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a) [-] the site of insertion is located in a selected gene, called the recipient gene, containing the complementing DNA encoding the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein or one of its biologically active derivatives and [in that];

b) [-] the polynucleotide coding for the P95/nucleolin, P40/PHAPIII and P30/PHAPI protein or one of its biologically active derivatives may comprise:

- [<<flanking sequences>>]flanking sequences on either side of the DNA to be inserted, respectively homologous to two genomic sequences which are adjacent to the desired insertion site in the recipient gene[.];

- the insertion DNA being heterologous with respect to the recipient gene, and;

- the flanking sequences being selected from those which constitute the above-mentioned complementing DNA and which allow, as a result of homologous recombination with corresponding sequences in the recipient gene, the reconstitution of a complete recombinant gene in the genome of the eukaryotic cell.

17. (Amended) A therapeutic composition comprising an antisense polynucleotide complementary to the nucleic acid sequence of P95/nucleolin, P40/PHAPIII and P30/PHAPI represented in Figure 49.

18. (Amended) A method for screening inhibitor molecules according to [anyoen] anyone of claims 1 to 12 comprising the steps of:

a) preparing a complex between the P95/nucleolin, P40/PHAPII and P30/PHAPI protein and a ligand that binds to the P95/nucleolin, P40/PHAPII and P30/PHAPI protein

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by bringing into contact the purified P95/nucleolin, P40/PHAPII and P30/PHAPI protein with a solution containing a molecule to be tested as a ligand binding to the P95/nucleolin, P40/PHAPII and P30/PHAPI protein;

b) visualizing the complex formed between the purified P95/nucleolin, P40/PHAPII and P30/PHAPI protein and the molecule to be tested.

23. (Amended) A method for screening inhibitor according to anyone of claims 2 to 12, comprising the following steps:

a) bringing into contact cells expressing the novel receptor according to the present invention at their surface with an amount of a HIV retrovirus equal to the $TCID_{50}$;

b) incubating said cells and retroviruses at 37°C during a period of time sufficient to allow the entry of the retrovirus within the cells, in the presence of a defined amount of the compound to be assayed;

c) washing the cells in order to remove the retroviruses that has been absorbed onto the membranes of the cells;

d) treating the cells in order to eliminate the remaining extracellular retroviruses, for example by a controlled proteolysis with trypsin;

e) preparing cytoplasmic extracts by treating the cells of step d) with an extraction buffer, for example with a buffer containing 20 mM Tris-HCl (pH7.6), 0.15 M NaCl, 5 mM [Mg Cl_2]$MgCl_2$, 0.2 mM PMSF, 100 U/ml aprotinin and 0.5% Triton X-100;

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f) centrifuging the cells obtained at step c), for example at 1000 g, and harvesting the supernatant medium, in order to separate the retroviral proteins;

g) detecting and optionally measuring the concentration of the HIV proteins, either directly or indirectly, for example by steric hindering.

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